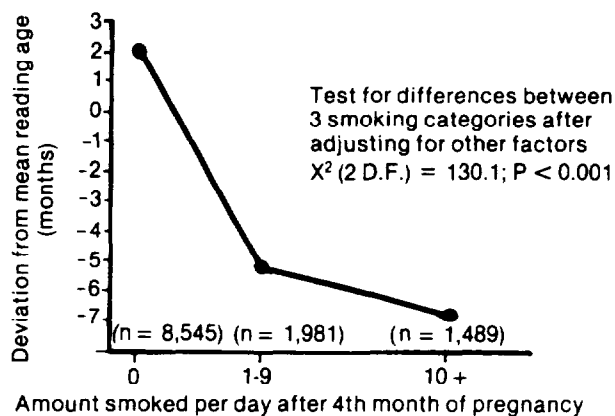
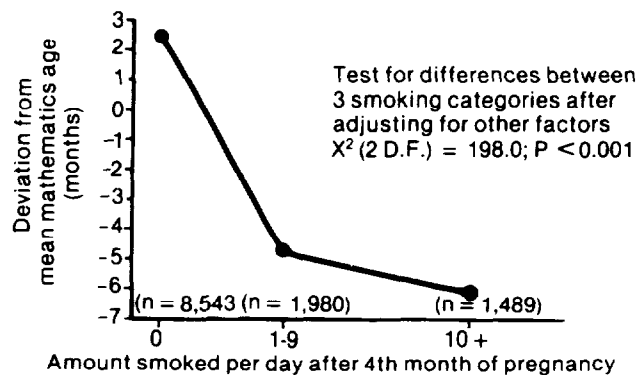


a) Reading Comprehension



b) Mathematics Ability



c) Height

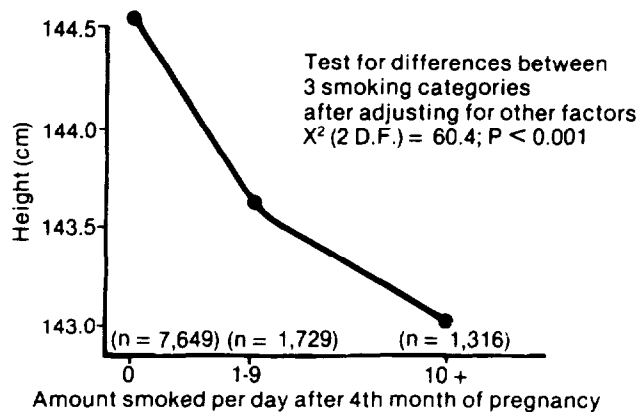


FIGURE 5.—Tests of 11-year-old children by mothers' smoking habits after the fourth month of pregnancy

SOURCE: Butler, N.R. (16).

hearing mechanism had occurred in infants of smokers, possibly due to a hypoxic effect of carbon monoxide on the cochlear organ during development (132).

These studies suggest unfavorable effects of maternal smoking during pregnancy on the child's long-term growth, intellectual development, and behavioral characteristics. Although these changes are difficult to study because of the vast complexity of possible antecedent and confounding variables, high priority should be given to obtaining conclusive answers about the long-term consequences of fetal exposure to cigarette smoke.

ROLE OF MATERNAL WEIGHT GAIN

In the search for mechanisms through which maternal smoking reduces birth weight, the question has been asked whether it might be an indirect result of reduced appetite, less intake of food, and lower maternal weight gain (84,127). Several early studies reported no differences between smoking and nonsmoking women in intake of food or in weight gain, and concluded that the effect of maternal smoking on birth weight was not mediated in this way (146).

Meyer analyzed the relationships between maternal smoking, birth weight, maternal weight gain, and gestation, using data based on 31,788 births from the Ontario Perinatal Mortality Study (106,107). She found a significant downward shift in the distribution of birth weights as maternal smoking level increased, but no similar shift in the distribution of maternal weight gain with smoking. Whereas the usual strong relationship between the proportion of births under 2,500 grams and maternal smoking level was found, there was no similar trend for the proportion of mothers who gained less than 10 pounds during pregnancy. Finally, the proportion of infants weighing less than 2,500 grams increased directly with the amount smoked within each maternal weight gain group from less than 5 pounds to 40 pounds or more, as shown in Figure 6 (83). From Figure 6, one might conclude that smoking has a more pronounced effect on low birth weight when maternal weight gain during pregnancy is less than 20 pounds.

Other studies have indicated a lack of relationship between smoking and maternal weight gain, while demonstrating a direct relationship between smoking and fetal growth rate. The German prospective study of 6,200 pregnant women, examined every month from the first trimester through delivery, showed no significant association between smoking habit and weight gain. The usual relationships were found between smoking and

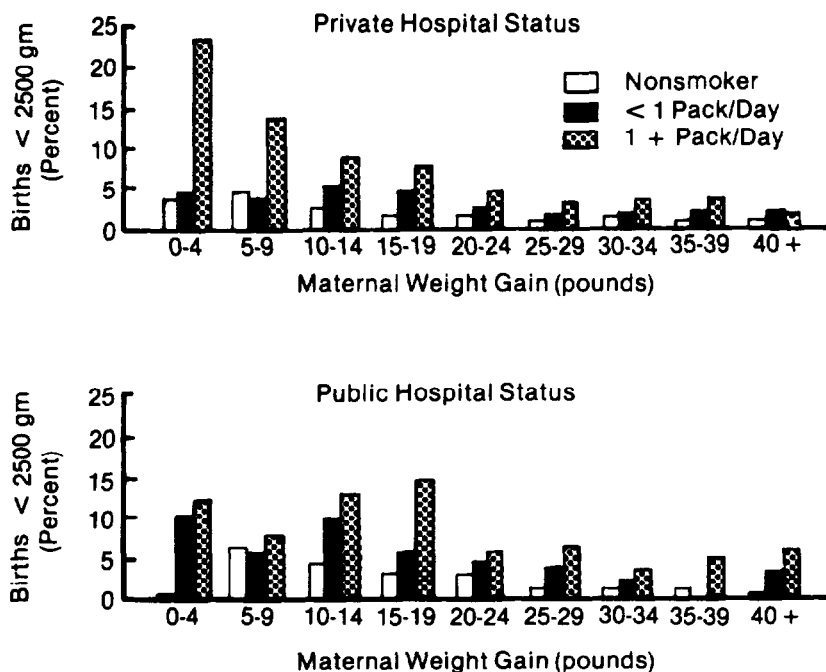


FIGURE 6.—Percentage of birth weights under 2,500 grams by maternal smoking level within maternal weight gain group (five-pound intervals) by hospital pay status. Births of 38+ weeks gestation (Ontario study)

SOURCE: Meyer, M.B. (83).

small-for-dates babies, with general retardation of weight, length, and head circumference in proportion to the number of cigarettes smoked during pregnancy (80). Miller and Hassanein also found that the effects of smoking on fetal growth did not appear to be related to maternal nutrition (93). Persson's study showing retardation of fetal growth of smokers' babies by serial measurement of biparietal diameters and by weight, length, and other measurements at birth showed that the low birth weights were independent of maternal weight gain. These authors concluded that the fetal growth retardation resulted from a direct pharmacological effect of smoking on the fetus "rather than an influence resulting from nutritional deprivation" (114).

Hajeri and colleagues studied maternal weight gain in 105 smokers of 10 or more cigarettes a day with a control group of nonsmokers who were similar with respect to gestation, age, height, parity, and maternal weight at conception. Birth weights, specific for sex, were significantly higher for infants of

TABLE 3.—Birth weight under 2,500 gm by maternal smoking and prepregnant weight

Prepregnant Weight	Total Births	Births < 2,500 gm per 100 Total Births				
		Maternal Smoking (Packs per day)			Ratio Smoker:Nonsmoker	
		0	< 1	1+	< 1	1+
< 120 lb (< 54 kg)	18,935	6.1	10.2	15.8	1.7	2.6
120–134 lb (54–61 kg)	19,798	4.2	6.3	9.5	1.5	2.3
135+ lb (> 61 kg)	10,456	3.3	5.1	8.7	1.6	2.6

SOURCE: Meyer, M.B. (86).

nonsmokers, with a mean difference for boys of 330 grams and for girls of 320 grams ($p < .01$). Mean extrauterine weight gain, calculated as the difference between maternal weight gain and the weights of fetus and placenta, was 7,044 grams for smokers and 6,899 grams for nonsmokers (49).

Garn has compared mean birth weights, specific for gestational age, of babies of obese smokers, all nonsmokers, and all smokers, using data from the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). Obesity was defined as the top 15 percent of the distribution of prepregnant weights, shown separately for black and white women. Babies of the 1,383 obese white smokers had mean birth weights similar to the total group of white nonsmokers and higher than the total group of white smokers. The 1,001 obese black smoking mothers had babies whose mean birth weights were generally higher than those of all black nonsmokers, leading Garn to conclude that "maternal obesity (weight-defined) apparently counteracts the smoking effect on the conceptus" (43). Because birth weight is strongly correlated with maternal size, a more appropriate comparison would have been between mean birth weights of the babies of obese smokers and the babies of obese nonsmokers. That such a comparison would show the usual relationship to maternal smoking level is suggested by Meyer's analysis of birth weight by maternal smoking and prepregnancy weight (Table 3). The correlation between maternal weight and the proportion of low-birth-weight babies is clear at each smoking level, and the independent relationship between smoking level and low birth weight is clear at each level of maternal weight.

TABLE 4.—Mean birth weights in successive pregnancies to the same women, by smoking habit

Smoking Habits First pregnancy	Smoking Habits Second pregnancy	Mean Birth Weight (gm)			Difference 2nd-1st (gm)
		N	# 1	# 2	
Smoker	Smoker	886	3204	3228	+24
Nonsmoker	Nonsmoker	988	3356	3388	+32
Difference: Nonsmoker - Smoker (gm)			+152	+160	
Smoker	Nonsmoker	119	3271	3381	+110
Nonsmoker	Smoker	108	3323	3265	-58
Difference: Nonsmoker - Smoker (gm)			+52	+116	

SOURCE: Naeye, R. (93).

The relative increases in the proportion of low-weight births with light and with heavy smoking are almost identical in the three strata of prepregnant weight (86).

Studies of birth weight, maternal weight, and maternal weight gain should also be carefully controlled for maternal age and parity. In studies of successive births to the same mother included in the Collaborative Perinatal Project of the NINCDS, Garn found that prepregnancy weights increased with successive pregnancies by similar amounts for smokers and nonsmokers (44). Naeye, using the same data base, reported that maternal weight gain was less in the second pregnancy than in the first pregnancy for smokers, for nonsmokers, and for women who changed habits between pregnancies in either direction (93). Second babies weighed on the average 24 grams more than first babies if the mother smoked both times, and 32 grams more if the mother smoked neither time (Table 4). If the mother smoked during the first and not during the second pregnancy, the second baby weighed an average of 110 grams more than the first baby; in women who smoked during the second pregnancy but not during the first pregnancy, second babies averaged 58 grams *less* than first babies (93).

The most careful analyses indicate that the effect of maternal smoking is a direct one not mediated through an effect on maternal appetite, eating, or weight gain. In conclusion, as stated in a Lancet editorial, "the appeal of the nutritional hypothesis is that women might be more readily encouraged to eat more during pregnancy than discouraged from smoking. . . . However, if,

as now seems more likely, the growth-retarding effect of smoking is due to fetal hypoxia, there is no short-cut to removing this adverse influence" (63). This conclusion in no way obviates the enormous importance of dietary factors during pregnancy.

Overt maternal malnutrition is associated with inadequate growth. Recently, it has been suggested that more subtle alterations in the maternal supply of essential nutrients combined with compromised uteroplacental circulation may contribute to reduced fetal growth. Crosby, et al. (26) observed that the concentrations of each of 14 amino acids and carotene were reduced significantly in the blood of smoking mothers. These workers postulated that, while these differences were on the order of 10 or 20 percent, they could be an important factor in producing the small-for-gestational-age infants associated with maternal smoking. In a study of over 1,100 pregnant women, Schorah, et al. (135) noted an inverse correlation between the number of cigarettes smoked and the leukocyte ascorbic acid concentration. For instance, the leukocyte ascorbic acid concentration was about 22 percent less in the blood of women who smoked more than 20 cigarettes a day as compared with controls. Despite a 15 percent increase in the number of circulating leukocytes in the blood of smokers, the blood ascorbic acid concentration was still 10 percent less than in controls. These differences were even more marked in women from lower socioeconomic groups. The authors suggested that in addition to the role of ascorbic acid in fetal nutrition, these lowered concentrations might be related to the increased incidence of premature rupture of the amniotic membranes in smoking women.

Smoking, Fetal and Infant Mortality, and Morbidity

SPONTANEOUS ABORTION

Past studies have demonstrated a statistically significant association between maternal cigarette smoking and spontaneous abortion (55,61,104), some showing a strong dose-response relationship (110,144,162). Spontaneous abortions are difficult to study because of problems of ascertainment. In prospective studies, early abortions may be missed, and bias may occur if one group tends to register earlier than the other. Retrospective studies allow more complete ascertainment but are subject to errors of recall. Nevertheless, higher rates of spontaneous abortion have been associated with maternal smoking in both types of studies (61,104,162).

Kullander and Kallen found higher rates of "spontaneous abortion" among smoking women, but noted that many of these

pregnancies were unwanted. Analysis of their data showed that the relative risk of spontaneous abortion of smokers compared with nonsmokers was 1.20 for wanted and 1.35 for unwanted pregnancies (61). A case-control study of spontaneous abortion with important variables held constant reported an 80 percent increase in the odds of smoking among the cases compared with controls (60).

Recent studies corroborated the finding of associations between smoking and spontaneous abortion risk. In a small retrospective study in New Zealand, Fergusson found that women who smoked more than 20 cigarettes a day had almost twice the nonsmoker risk of having had a previous spontaneous abortion, and that the association could not be explained by differences in maternal age, educational level, parity, race, socioeconomic status or marital status (42). In a study of 12,013 consecutive pregnancies in Dublin, Ireland, Murphy and Mulcahy found a positive association between the number of cigarettes smoked and the rates of spontaneous abortion, independent of the effects of maternal age and parity. The authors stated that induced abortions are a negligible factor in Ireland and concluded that maternal smoking leads to reduced reproductive efficiency at all stages of pregnancy (92). Himmelberger and colleagues surveyed a group of professional women in medicine concerning the influence of maternal smoking on their 12,194 pregnancies (54). After controlling for interfering variables, the risk of spontaneous abortion for certain subgroups of heavy smokers was estimated to be as much as 1.7 times that for nonsmokers. Spontaneous abortion rates were lowest in the 25 to 29 year old category, increasing with age to levels of 33 and 36 percent for nonsmokers and smokers, respectively, at age 40 plus. The relative increase in risk associated with maternal smoking was highest at the youngest ages and decreased with increasing age (54).

An editorial in the British Medical Journal summarized these findings and stated: "Cigarette smoking, one of the first manifestations of women's social emancipation, is emerging as a possible threat to her procreative role." The proportion of abnormal karyotypes in abortuses of women who smoke appears to be reduced rather than increased (1). The mechanism underlying the smoking-related excess appears to be due to complications of pregnancy rather than to any fetal abnormality (13).

CONGENITAL MALFORMATIONS

Several studies have reported perinatal, fetal, or neonatal mortality rates by cause. In these comparisons, death rates due

TABLE 5.—Incidence of congenital abnormality (all single births)

	Nonsmokers		Smokers	
	Number	Percent	Number	Percent
Total abnormal infants		2.37		2.73
Type of abnormality				
Anencephaly	18	0.2	15	0.2
Spina bifida	20	0.22	23	0.3
Other C.N.S. abnormality	38	0.42	36	0.47
Cardiovascular abnormality	34	0.37	32	0.42
Gut abnormality	21	0.23	24	0.32
Genito-urinary abnormality	39	0.43	25	0.33
Bone abnormality	65	0.72	52	0.68
Cleft palate and/or hare lip	10	0.11	20	0.26
Other abnormality	19	0.21	18	0.24

χ^2 (all abnormalities) = 2.22, $p > 0.05$.

χ^2 (cleft palate and hare lip) = 5.36, $0.01 < p < 0.05$.

SOURCE: Andrews, J. (3).

to congenital malformations have usually been lower for smokers' than for nonsmokers' infants (3,22,46,87). This is compatible with the finding that smoking-related spontaneous abortions have a lower frequency of abnormal karyotypes and tend to occur later than spontaneous abortions in nonsmokers. As previously described, increased losses of conceptus associated with maternal smoking appear to be due to pregnancy problems and complications rather than to abnormalities of the embryo or fetus (41). Andrews and McGarry, in a community study of 18,631 pregnancies in Cardiff, Wales, reported that smokers' infants had lower mortality rates from malformations than those of nonsmokers. Rates of stillbirths due to congenital malformations were 0.32 and 0.27 per 100 nonsmokers and smokers respectively. Corresponding rates for neonatal deaths were 0.33 and 0.31 per 100 babies of nonsmoking and smoking mothers. On the other hand, the incidence of congenital malformations among all single births in Andrews' population was higher among smokers' babies, overall, and specifically higher for cleft palate and lip. Among other sites, some were higher for smokers and some for nonsmokers, as is shown in Table 5 (3).

A significant positive association between cardiac malformations and maternal smoking was shown by Fedrick and colleagues, based on firm diagnoses among stillbirths, neonatal deaths, and survivors to age 7 from the British Perinatal Mortality Survey. However, this difference was largely due to the inclusion of patent ductus arteriosus, which may or may not be classified as a malformation (80).

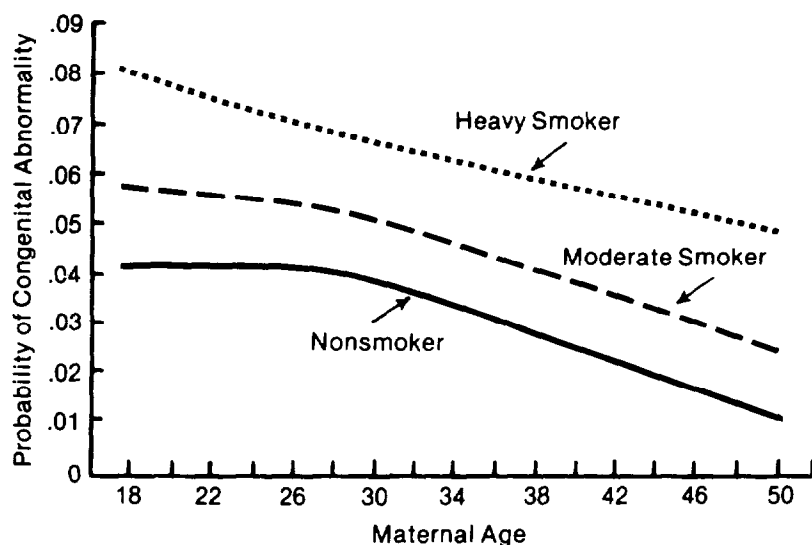


FIGURE 7.—Risk of congenital abnormality according to age and smoking habit

SOURCE: Himmelberger, D.U. (54).

Some recent studies have shown a positive association between maternal smoking and congenital malformations, defined in a variety of ways. Himmelberger and colleagues carried out a mail survey of professional women in medicine (54). They were interested in exposure to anesthetic gases in the operating room, and evaluated possible effects on pregnancy outcome of a number of factors including cigarette smoking. Information was obtained and analyzed by a multiple logistic regression based on 12,914 pregnancies, including 10,523 live births, which represented a response rate of 53.2 percent. After the effects of age, exposure to anesthetic gases, and pregnancy history were controlled, the risk of congenital abnormalities for babies of mothers who smoke was estimated. A statistically significant risk ($p < .05$) for maternal smoking was found. Figure 7 shows the estimated risk of congenital abnormality as a function of maternal age for nonsmokers, moderate smokers (1 to 19 per day), and heavy smokers (20 plus per day). Relative risks for heavy smokers compared with nonsmokers were as high as 2.3. Rates of abnormalities in each general category were higher for the children of smokers (see Table 6). The significant increase in cardiovascular abnormalities among smokers' children is in agreement with Fedrick's findings (40) and in general agree-

TABLE 6.—Comparison of congenital abnormality rates for babies born of smokers and nonsmokers, by type of abnormality

Abnormality	Smokers		Nonsmokers		p*
	%	No.	%	No.	
Cardiovascular	19.07+	(68)	13.65	(95)	0.02
Respiratory	15.15	(54)	12.07	(84)	0.10
Musculoskeletal	23.84	(85)	19.69	(137)	0.08
Gastrointestinal	13.46	(48)	9.48	(66)	0.04
Central nervous system	11.50	(41)	10.20	(71)	0.27
Urogenital	21.32	(76)	15.81	(110)	0.02

*One-tail significance level for the test of the difference between two proportions.

+Rate is number of congenital abnormalities per 1,000 live births. Rates based upon 3,565 live births among the smokers and 6,958 live births among the nonsmokers.

SOURCE: Himmelberger, D.U. (54).

ment with the study of Andrews and McGarry (3). Himmelberger, et al. point out that their findings are based on retrospective survey data, obtained by mail, and therefore subject to bias from various sources, including that of a high nonresponse rate. However, the study methods have been designed to eliminate those effects (54).

A recent study by Borlee and Lechat controlled for confounding variables by matching births with congenital malformations to control births according to hospital and time of birth, maternal age, sex of child, and socioeconomic level of parents. Two hundred and two children with malformations diagnosed at birth were compared with 175 controls, from a total of 17,970 consecutive births studied from June 1972 through May 1974. No differences were found between cases and controls in the distribution of smoking habits, including the number of cigarettes smoked with or without filters. Sixty-six percent of mothers of malformed infants and 68 percent of mothers of controls were nonsmokers. Fathers' smoking habits were also similar among cases and controls. Significantly more mothers of malformed infants were heavy coffee drinkers (8 plus cups per day). Because of the frequent association between heavy coffee drinking and smoking, both habits should be included in studies of environmental factors possibly related to the risk of congenital malformations (10). The same is true for consumption of alcohol in populations where drinking is prevalent.

Mau and Netter have reported births by gestation, birth weight, perinatal mortality, and the incidence of congenital malformations by smoking habits of fathers in 3,696 cases in

which the mother was a nonsmoker. Trends toward lower birth weights and more preterm births with increasing levels of paternal smoking were not statistically significant. In the total study of 5,200 births, regardless of maternal smoking habits, there was a significant increase in the incidence of severe malformations with increasing levels of paternal smoking; children of heavily smoking fathers had about twice the expected incidence. Although malformations in all systems were more frequent if the father smoked over 10 cigarettes per day, only the differences in facial malformations were significantly different ($p < .01$) by smoking level. The authors state that the trends with paternal smoking were independent of maternal smoking level, maternal and paternal age, and social class (120).

More studies of these possible relationships are urgently needed. As serious malformations are relatively rare, the case-control approach is probably the method of choice, with careful matching of cases with suitable controls.

PERINATAL MORTALITY

The 1973 report, *The Health Consequences of Smoking* and the 1979 Report have summarized studies demonstrating a direct relationship between level of maternal smoking and risk of perinatal loss. The reports have also clarified reasons for the variation in risk observed in these studies (146,147).

Two important reasons for variability between studies have been demonstrated. First, other important variables such as age, parity, race, and socioeconomic status influence the results if they are unequally distributed between comparison groups of smokers and nonsmokers (89). Second, cigarette smoking is more harmful to the pregnancies of certain women than to those of others. In general, women with other risk factors were at greater risk from smoking than otherwise low-risk women (3,15,22,128,144,159).

Table 7 illustrates these points. It shows that women characterized by low social class, low level of education, being very young or old during pregnancy, or being black, have higher risks of perinatal mortality than their counterparts. Their increase in risk due to smoking is relatively greater. Meyer, et al. measured the perinatal mortality risks of light smokers (less than a pack of cigarettes per day) and of heavy smokers (one pack or more per day) relative to nonsmoker risks within subgroups of the population. The increased risk of perinatal mortality for light smokers who were young, low-parity, and non-anemic was less than 10 percent. At the other extreme, mothers characterized by high-parity, public hospital status, previous

TABLE 7.—Examples of perinatal mortality by maternal smoking status related to other subgroup characteristics

Study Population	No. of births		Category	Perinatal or neonatal deaths/1,000 births		Relative risk*
	Non-Smokers	Smokers		Non-smokers	Smokers	
British Perinatal Mortality Survey, England, all births	11,145	4,660	Social class 1,2 (high) 3-5	25.8	26.3	1.02
				33.5	46.6	1.39
Washington Co. Maryland, white	7,646	4,641	Father's education 9+ years ≤ 8 years	14.4†	16.1†	1.12
				17.6†	38.0†	2.16
Northern Finland, white	8,898	2,346		23.2	23.4	1.01
California, middle to upper middle class	6,067	3,726	Race			
	2,219	1,071	White Black	11.0† 17.1†	11.3† 21.5†	1.03 1.26
Boston City Hospital Prenatal Clinic	513	892	Race			
	1,225	636	White Black	29.2 28.6	31.4 54.1	1.08 1.89
Quebec, 10% sample of registered births	3,912	2,967	Maternal age			
			<25	12.1	16.1	1.33
			25-34	12.6	13.2	1.05
			35+	23.0	41.7	1.81

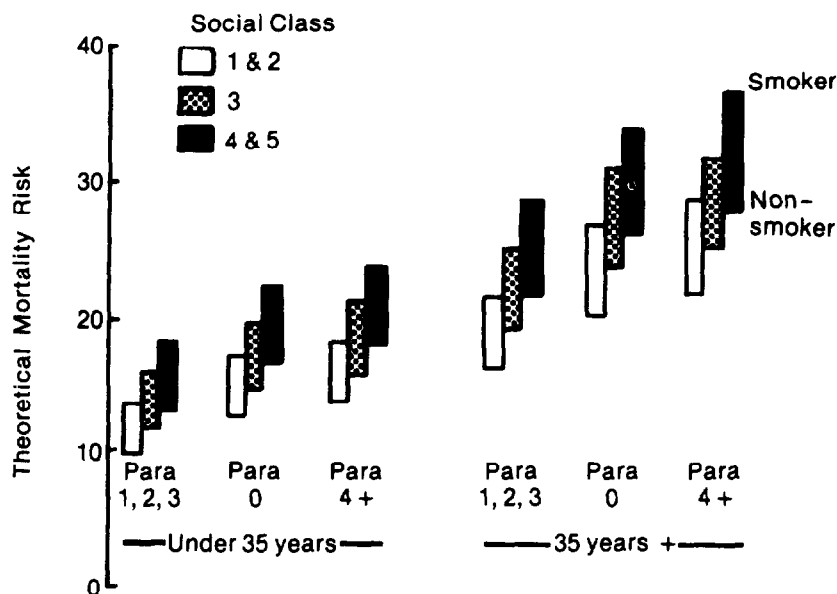


FIGURE 8.—Theoretical cumulative mortality risk according to smoking habit, in mothers of different age, parity, and social class groups

SOURCE: Butler, N.R. (15).

low-weight births, or anemia had an increased perinatal mortality risk of 70 to 100 percent when they were heavy smokers (88).

To help visualize the interacting effects of maternal smoking and of other factors on perinatal mortality risk, Butler has calculated theoretical mortality risks based on data from the British Perinatal Mortality Study. In Figure 8, perinatal mortality risks by social class, maternal age, and parity are arranged in order of increasing magnitude. The differences between smokers' and nonsmokers' risks are represented by the height of the bars, which varies depending on other risk factors (15).

These studies show that the risk of spontaneous abortion, of fetal death, and of neonatal death increases directly with increasing levels of maternal smoking during pregnancy. Studies of smoking during pregnancy show a range of perinatal mortality risk ratios (smokers versus nonsmokers) from a low of 1.01 to a high of 2.42. Variability between risk ratios in different study populations may be due to lack of comparability between smokers and nonsmokers in other respects, or to interaction between smoking and other pregnancy risk factors. Studies failing to

take account of other important variables may show unusually high or unusually low risk ratios.

CAUSE OF DEATH

The increased perinatal mortality associated with maternal smoking is concentrated within a few cause-specific categories. Excess stillbirths have been associated with antepartum hemorrhage or abruptio placentae and with "unknown cause" (3,46). Excess neonatal deaths were associated with immaturity, asphyxia, atelectasis (23), and with the respiratory distress syndrome (3).

Meyer and Tonascia (87) analyzed fetal and neonatal deaths to identify causes of death which showed an excess if the mother smoked. Fetal and neonatal deaths by coded cause and maternal smoking habit are shown in Table 8. For each cause the observed numbers for smokers were compared with the number expected at nonsmoker rates. The differences between observed and expected numbers indicate the number of deaths in each category attributable to maternal smoking.

Fetal deaths showed a major smoking-related excess in the category of "unknown" cause and some increase from "anoxia" and "maternal cause." By contrast, neonatal deaths related to smoking were in the category of "prematurity alone," or in the related category of "respiratory difficulty." The tentative conclusion to be drawn here is that fetuses and neonates whose deaths were related to maternal smoking had no recognizable pathology, but had died *in utero* from anoxia, maternal cause, or unknown cause, or had suffered the consequences of preterm delivery.

Complications of Pregnancy and Labor

Studies have consistently found a direct relationship between maternal smoking level and the incidence of placenta previa, abruptio placentae, bleeding during pregnancy, and premature rupture of membranes (3,24,46,61,86,87,94,95,130,144,145). The association is independent of socioeconomic and racial background (144), parity (3) and many other factors (86) (Figure 8).

These complications carry with them a high risk of fetal and neonatal loss, and are frequently cited as the cause of death among the offspring of women who smoke. Kullander and Kallen found a significant increase in the frequency of abruptio placentae among smokers' children dying before the age of 1 week (61). In a prospective study of 9,169 pregnancies by Goujard and colleagues, a large proportion of the increase in stillbirths among smokers was caused by abruptio placentae (46).

TABLE 8.—Fetal and neonatal deaths by coded cause and maternal smoking habit (Canadian English-speaking mothers)

Coded cause	Observed		Expected smoker*	Observed Expected difference	p+ value
	Nonsmoker	Smoker			
Fetal deaths					
Unknown	75	125	81.4	43.6	0.003
Malformations	32	24	34.7	-10.7	N.S.
Hemolytic disease	11	15	11.9	3.1	N.S.
Anoxia	16	29	17.4	11.6	N.S.
Maternal cause	31	45	33.4	11.3	N.S.
All others	8	13	8.7	4.3	N.S.
Total	173	251	187.9	63.1	0.003
Neonatal deaths					
Unknown	52	51	56.5	-5.5	N.S.
Malformations	22	24	23.9	0.1	N.S.
Hemolytic disease	7	8	7.6	0.4	N.S.
Respiratory difficulty	46	63	50.0	13.0	N.S.
Prematurity alone	33	65	35.8	29.2	0.005
Maternal cause	2	6	2.2	3.8	N.S.
All others	16	16	17.4	-1.4	N.S.
Total	178	233	193.3	39.6	0.06
Total Births	15,240	16,549			

N.S. = not significant.

*Based on nonsmoker rate.

p+ value derived from chi square based on a null hypothesis of no difference between smokers and nonsmokers.

SOURCE: Meyer, M.B. (87).

Naeye reviewed the clinical and postmortem material from the 3,897 fetal and infant deaths in the Collaborative Perinatal Project of the NINCDS (102) and reported an association between perinatal mortality rates caused by abruptio placentae and number of cigarettes smoked by the mother (95). Abruptio placentae was the underlying cause identified in 11 percent of all the deaths in this large study (94).

Analysis of data from the Ontario Perinatal Mortality Study corroborated these findings. Increasing levels of smoking resulted in a highly significant increase in the risks of placental abruptions, placenta previa, bleeding in pregnancy, and premature and prolonged rupture of membranes. Fetal and neonatal deaths were analyzed for associations between them and smoking-related excesses of various coded complications of pregnancy and labor. Although most diagnoses showed no association with excess mortality for smokers' babies, a few stood

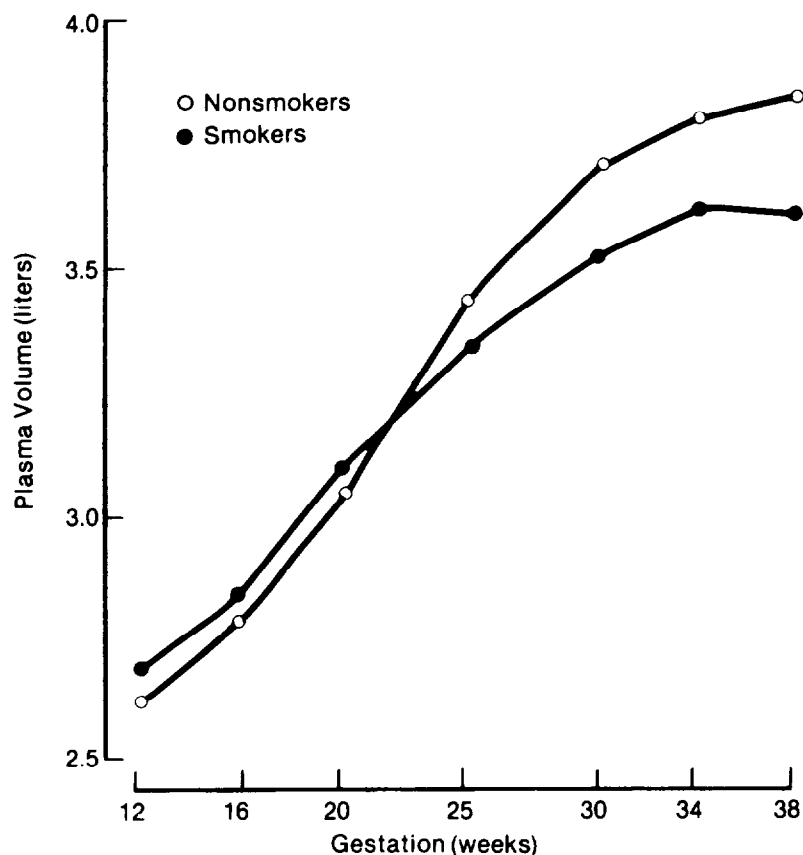


FIGURE 9.—Mean plasma volume in nonsmokers and smokers

SOURCE: Pirani, B.B.K. (117).

out as highly significant. Excess fetal deaths of smokers' babies were strongly associated with bleeding during pregnancy, either before ($P = 0.01$) or after ($p = 0.0005$) 20 weeks gestation. In other coded categories, a significant excess of fetal deaths occurred among smoking mothers with abruptio placentae ($p = 0.0001$) or other obstetrical problems. Similar comparisons were made for neonatal deaths. A strong, significant relationship between smoking-related excess neonatal deaths and a history of bleeding before 20 weeks of gestation was found ($p = 0.0001$). Other categories that showed significant increases of smoking-associated neonatal deaths were the admission status of rupture of membranes only, other obstetrical complications, and duration of rupture of membranes over 48 hours (87).

PREECLAMPSIA

Several published studies have reported that the incidence of preeclampsia is declining as the number of cigarettes smoked increases (109,145). Data from the British Prenatal Mortality Study were cross-tabulated by parity, severity of preeclampsia, and maternal smoking status. Smokers had lower rates of all grades of preeclampsia than nonsmokers, whether they were primiparae or multiparae (15). Andrews and McGarry showed that the inverse relationship between cigarette smoking and preeclamptic toxemia was independent of social class, maternal weight before pregnancy, and maternal weight gain during pregnancy (3). Despite this effect of smoking on the incidence of preeclampsia, there is a greatly increased risk of perinatal mortality if preeclampsia does develop in a smoker (3,34,129). Several authors have suggested that this negative association may be due to the hypotensive effect of thiocyanate, which is derived from the cyanide present in cigarette smoke and is regularly found in the blood of smokers (3,109). Because preeclampsia is predominantly a complication of first pregnancies, it is possible that the occasional finding of reduced rates of perinatal mortality in young, primiparous, light smokers who are otherwise healthy is due to this relationship.

Pirani and MacGillivray performed seven serial measurements from the end of the second trimester until term in 31 nonsmokers and 29 smokers. After 25 weeks gestation the plasma volume of smokers failed to keep pace with that for nonsmokers, the increases in volume being 25 percent less in smokers (Figure 9). Plasma volume and total body water expansion are related to birthweight, at least in primigravidas. After 30 weeks of gestation, total body water in smokers plateaued in contrast to nonsmokers, so that by term their body water volume increase was about 25 percent less. Serum heat-stable alkaline phosphatase levels in smokers significantly exceeded the concentration in nonsmokers from the 37th week of pregnancy onward. This enzyme is of placental origin, and cigarette smoking may contribute to this change by its effects on the placenta (117).

Whether the reduction in the incidence of preeclampsia with maternal smoking is due to the hypotensive effects of thiocyanate, to the reduced size of the baby, to a smaller increase in maternal blood volume, or to another process requires further study.

PRETERM DELIVERY, PREGNANCY COMPLICATIONS, AND PERINATAL MORTALITY BY GESTATION

Studies of large numbers of births to measure mean gestation by smoking habit have demonstrated differences of only a day

or two. This finding led to the conclusion that maternal smoking does not affect gestation (14,52,74,102,146,159). On the other hand, abundant evidence has been presented that a smoking-related increase in preterm delivery plays an important role in the increased risk of neonatal death for infants of smokers.

When the proportion of preterm births is measured, rather than the mean gestation, smokers have shown consistently higher rates than nonsmokers, as illustrated in Table 9. In four studies in which all births and perinatal deaths were included, the risk of early delivery increased from 36 to 47 percent if the mother smoked, and 11 to 14 percent of all preterm births could be attributed to maternal smoking (3,15,38).

Figure 10, using data from the Ontario Perinatal Mortality Study, shows percentage distributions by gestational age of births to nonsmokers, light smokers, and heavy smokers, plotted on a semilogarithmic scale to emphasize differences between smoking-level groups in very preterm births. There is little difference between the means of these curves because the great majority of births occur around term in all groups. There is, however, a significant and dose-related increase in the proportions of preterm babies born to women who smoke. These preterm deliveries account for a small proportion of total births but for a large proportion of the deaths (82,146).

As previously reviewed, Meyer and Tonascia have related the excess fetal and neonatal mortality of smokers' infants and the excess incidence of pregnancy complications among women who smoke to the gestational age of occurrence, using a life-table approach. A starting population of all pregnancies *in utero* at 20 weeks was used to calculate the probabilities of fetal death, live delivery followed by survival or death, or the occurrence of a complication followed by fetal death or delivery. At 28 weeks (the next point defined by the data), the population at risk included those remaining *in utero* at that point. Figure 11 shows the probability of perinatal death during each period of gestational age starting at 20 weeks. Risks for smokers' infants were significantly greater in the earlier weeks, but not different after 38 weeks gestation (87,146).

A similar approach was applied to determine the risk by gestation of abruptio placentae, placenta previa, and premature rupture of membranes for smokers and nonsmokers. The risk of all these complications was higher for smokers throughout gestation, but in all the differences were most significant in the weeks of pregnancy from 20 to 32 or 36 weeks (87,146). The lower limit of 20 weeks was built into the study design, which included all single births of at least 20 weeks gestation (106,107).

These studies show that excess deaths of smokers' infants are

TABLE 9.—Preterm births by maternal smoking habit: relative and attributable risks, derived from published studies

Study	Smokers (proportion)	Preterm Births* per 100 Total Births		Relative Risk Smokers/Non- smokers	Attributable Risk %
		Nonsmokers	Smokers		
Cardiff	.465	6.7	9.2	1.36	14
Great Britain	.274	4.7	6.9	1.47	11
Montreal	.432	7.7	10.6	1.38	14
Ontario	.435	7.4	10.1	1.36	14

*Cardiff and Ontario data are for <38 weeks. All others are for <37 weeks.

SOURCE: Andrews, J. (3), Campbell, J.M. (15), Fabia, J. (38), Meyer, M.B. (86), U.S. Department of Health, Education, and Welfare (146).

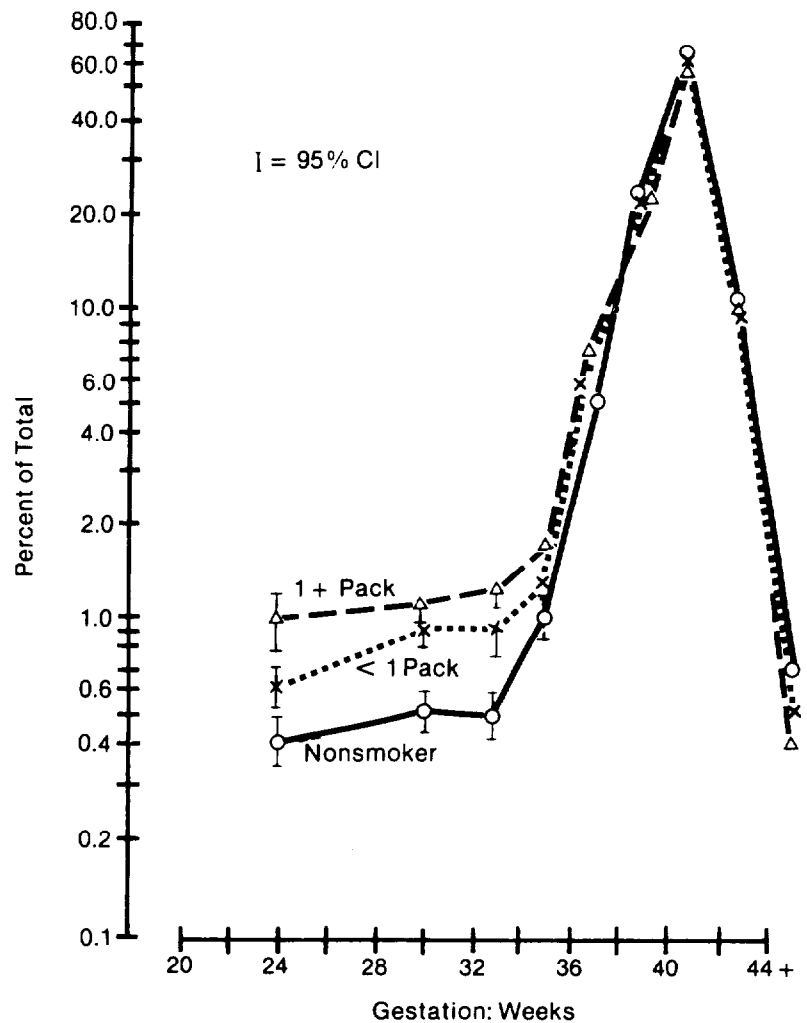


FIGURE 10.—Percentage distribution by weeks of gestation of births to nonsmokers, smokers of less than one pack per day, and smokers of one pack per day or more

SOURCE: Meyer, M.B. (82).

found mainly in the coded cause categories of “unknown” and “anoxia” for fetal deaths, and in the categories of “prematurity alone” and “respiratory difficulty” for neonatal deaths. This finding indicates that the excess deaths result not from abnormalities of the fetus or neonate, but from problems related to

220

the pregnancy. Increasing levels of maternal smoking result in a highly significant increase in the risks of placental abruptions, placenta previa, bleeding early or late in pregnancy, premature and prolonged rupture of membranes, and preterm delivery, all of which carry high risks of perinatal loss. Although there is little effect of maternal smoking on mean gestation, the proportion of fetal deaths and live births that occur before term increases directly with maternal smoking level. Up to 14 percent of all preterm deliveries in the United States may be attributable to maternal smoking. According to the results of one large study, the most significant difference between smokers' and nonsmokers' risk of perinatal mortality and pregnancy complication occurs at the gestational ages from 20 to 32 or 36 weeks.

These findings lead to the conclusion that maternal smoking can be a direct cause of fetal or neonatal death in an otherwise normal infant. The immediate cause of most smoking-related fetal deaths is probably anoxia, which can be attributed to placental complications with antepartum bleeding in 30 percent or more of the cases. In other cases, the oxygen supply may simply fail from reduced carrying capacity and reduced unloading pressures for oxygen caused by the presence of carbon monoxide in maternal and fetal blood. Neonatal deaths occur as a result of the increased risk of early delivery among smokers, which may be secondarily related to bleeding early in pregnancy and premature rupture of membranes (146).

Long-Term Morbidity and Mortality

Studies of infant and child morbidity and mortality by the mother's smoking habits usually cannot distinguish between the effects of smoking during pregnancy and the effect of the infant's or child's passive exposure to cigarette smoke after birth. Several studies have found that hospitalization rates for pneumonia and bronchitis were higher during the first year of life for infants of smoking mothers (20,21,53). Rates in children were higher if the smoking parents also had cough and phlegm. Harlap and Davies found that the risk of contracting pneumonia or bronchitis in the first year of life more than doubled if the parents smoked more than 24 cigarettes a day (53).

A unique and important study of morbidity and mortality in smokers' and nonsmokers' children up to the age of five has now been published by Rantakallio (119). The experience up to age 5 of over 12,000 children born in 1966 in Northern Finland, comprising 96 percent of all births in two provinces, was ascertained through hospital and death records and questionnaires. Smok-

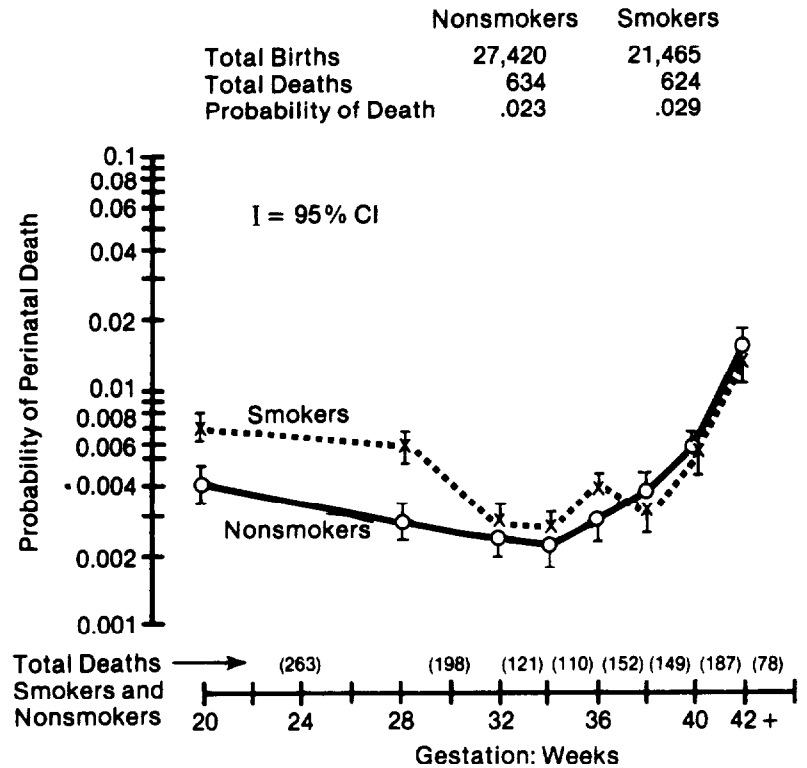


FIGURE 11.—Probability of perinatal death for smoking and nonsmoking mothers, by period of gestational age (bars show 95% confidence intervals)

SOURCE: Meyer, M.B. (87).

ing was rare in this population, and the smokers tended to be young and otherwise healthy. Fourteen percent of pregnant women smoked fewer than 10 cigarettes per day (mean number after the second month of pregnancy 3.9) and 3 percent smoked more than 10 cigarettes per day (mean number 12.2); the remaining 83 percent of the population were nonsmokers. It was therefore possible to remove the usual problems of confounding variables by close individual matching of 1,750 smokers to nonsmoking "controls". Matching factors included marital status, maternal age within 2 years, and place of residence, with the latter category including many socioeconomic variables to equalize the probable use of medical facilities and other differences. Although the author states that perinatal mortality did not show a statistically significant increase for smokers,

rates were 24 per thousand for controls, 26 per thousand for light smokers, and 33 per thousand for "heavy" smokers (defined as smoking 10 plus cigarettes per day). These rates are similar to those found in other studies in which differences were statistically significant. Postneonatal mortality, from 28 days to 5 years, was higher for smokers' children with rates of 11.1 and 3.9 per thousand for smokers' and nonsmokers' children respectively. Overall death rates of 24.7 per thousand births in smoking women and 16.5 per thousand births in nonsmoking women were reported for children under the age of 5, of which 12.6 and 8.8 were neonatal.

In addition, the children of the smokers were hospitalized more frequently, had more visits to doctors, and had longer average durations of hospital stays than children of nonsmokers. Respiratory diseases caused significantly more hospitalizations among smokers' children. It is of great interest that the children born to a subgroup of women who stopped smoking during the last 3 months of pregnancy showed no increase of postneonatal mortality or morbidity up to the age of 5, compared with controls. However, these women had been very light smokers before quitting. Table 10, derived from Rantakallio's study, shows that the various outcomes measured show increasing rates of morbidity and mortality with increasing levels of smoking. However, it may not be possible to distinguish between the adverse effects of maternal smoking during pregnancy and the adverse effects on infants and children exposed to cigarette smoke in the home, because women who smoked during pregnancy probably also continued to smoke after pregnancy.

Because of the known carcinogenic potential of tobacco smoke and the evidence that benzo(a)pyrene reaches the placenta, Neutel and Buck investigated the relationship of maternal smoking during pregnancy to the incidence of cancer in children aged 7 to 10. A combined population of 89,302 births from the Ontario Perinatal Mortality Study and the British Perinatal Mortality Survey was used as a base population for a prospective study in which 65 cancer deaths and 32 cancer survivors were identified. For cancer of all sites, the children of smokers had a relative risk of 1.3, with 95 percent confidence limits of 0.8 to 2.2. A dose-response relationship was not observed. The numbers were not large enough to determine significant differences by site. Excess cancer rates for children of mothers who smoke and a possible dose-related progression were concentrated at ages 0 to 24 months, but these rates were based on small numbers of cases. The authors conclude that "although a significant excess is not demonstrable, a doubling of the cancer risk for children of smokers cannot be ruled out." Their equivocal re-

TABLE 10.—Long term effects of morbidity and mortality by level of maternal smoking

A. Mortality				
	Nonsmokers Control 1	Control 2	Light Smokers (1-10 per day)	Heavy Smokers (10 + per day)
Number of children	1300	258	1302	252
Doctor visits per child (mean number)	.71	.61	.76	.83
Hospitalizations per child (mean number)	.19	.15	.22	.39
< Age 1	.14	.08	.17	.30
Age 1-5	.15	.17	.22	.25
B. Perinatal and postneonatal mortality (28 days to 5 years) per 100 births, by maternal smoking				
	Nonsmokers		Smokers	
	Control		Light	Heavy
Total births number	1844			
Perinatal mortality per 1,000 births	23.9		25.7	32.6
Postneonatal mortality	3.9			
All mortality per 1,000 live births	16.5			

SOURCE: Rantakallio, P. (119).

sults were reported to encourage other workers to add to the data (99). This should certainly be done, with particular emphasis on the first 2 years of life.

Rantakallio, et al. also analyzed the use rates of ophthalmological services in their follow-up study of approximately 12,000 children, relating these rates of prenatal factors ascertained during pregnancy. The incidence of squint among smokers' children was 22.5 per thousand, compared with 11.5 per thousand among the children of matched, nonsmoking controls ($p < .05$). On the other hand, rates of dacryostenosis and of other congenital ocular malformations were higher among the children of controls. The authors state that squint was inversely correlated with birth weight and was more common among children with other diseases, especially nervous or mental diseases (121).

SUDDEN INFANT DEATH SYNDROME

Maternal smoking habits have been ascertained in several studies of the sudden infant death syndrome (SIDS). In all of these, an association has been found between maternal smoking during pregnancy and the incidence of sudden infant death. Steele and Langworth, in a study of 80 cases, each with two matched controls, which were traced back to the Ontario Perinatal Mortality Study population of 1960-61, found that sudden infant deaths were strongly associated with the frequency and level of maternal smoking during pregnancy ($p < .001$). Thirty-nine percent of the cases were nonsmokers versus 60 percent of controls; 36 percent of the cases and 27 percent of the controls smoked less than a pack per day; 24 percent of the cases and 10 percent of the controls smoked a pack per day or more. The habits of the remaining 1 to 2 percent of mothers were unknown (139).

Bergman and Wiesner studied 56 families who lost babies to the sudden infant death syndrome and 86 control families. They reported that a higher proportion of SIDS mothers smoked during pregnancy than controls (61 percent versus 42 percent), more smoked after pregnancy (59 percent versus 42 percent), and SIDS mothers smoked a significantly greater number of cigarettes than controls. These authors indicate that exposure to cigarette smoke (passive smoking) appears to enhance the risk for SIDS for reasons not yet known (8). However, whether prenatal or postnatal exposure is more important cannot be determined.

Naeye, et al., in their analysis of 125 SIDS victims from the population of the Collaborative Perinatal Project of the